CLAIMS

We claim:

1. A method of treating a drug resistant phenotype comprising administering a sigma-1 receptor ligand to a subject in an amount sufficient to restore drug sensitivity.

2. The method of claim 1, wherein the sigma-1 receptor ligand is a (+)enantiomer.

3. The method of claim 1, wherein the sigma-1 receptor ligand is selected from the group consisting of (+)pentazocine, (+)*N*-allylnormetazocine, 2-(4-morpholinethyl)-1-phenylcyclohexanecarboxylate, *cis*-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)cyclohexylamine, and *N*-[2-3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-azapinyl)ethylamine dihydrochloride.

4. The method of claim 1, wherein the subject is undergoing a treatment regime with one or more chemotherapeutic agents.

5. The method of claim 4, wherein the chemotherapeutic agent is selected from the group consisting of actinomycin D, doxorubicin, mitoxantrone, paclitaxel and vincristine.

6. The method of claim 4, wherein the chemotherapeutic agent is doxorubicin.

7. The method of claim 4, wherein the chemotherapeutic agent is paclitaxel.

8. The method of claim 4, wherein the chemotherapeutic agent is doxorubicin and the sigma-1 receptor ligand is (+)pentazocine.

9. The method of claim 4, wherein the chemotherapeutic agent is paclitaxel and the sigma-1 receptor ligand is (+)pentazocine.

10. A method for reducing a drug resistant phenotype *ex vivo* comprising treating a cultured cell with a sigma-1 receptor ligand in an amount sufficient to restore drug sensitivity.

11. The method of claim 10, wherein the cell is undergoing unwanted proliferation.

12. The method of claim 11, wherein the cell is resistant to one or more chemotherapeutic agents.

13. The method of claim 11, wherein the cell is obtained from a tissue source selected from the group consisting of brain, uterine, blood, breast, thyroid, pancreas, gastrointestinal, ovarian, prostate, lung, skin and lymphatic tissue.

14. A method of increasing drug sensitivity comprising administering a sigma-1 receptor ligand to a subject in an amount sufficient to down regulate P-glycoprotein expression in a population of drug resistant cells.

15. A method of attenuating a potentially drug resistant phenotype comprising the steps of:

1) contacting a cell with a sigma-1 receptor ligand
2) contacting a cell with a drug
3) maintaining drug sensitivity in the cell.

16. A method of reducing P-glycoprotein expression in a cell comprising the steps of:

1) contacting a cell with a sigma-1 receptor ligand;
2) binding the sigma-1 receptor ligand to the sigma-1 receptor;
3) reducing P-glycoprotein expression in the cell.

17. A method of screening compositions for tolerance-reducing activity comprising the steps of:

1) contacting a test cell that expresses high levels of P-glycoprotein with a composition potentially comprising a sigma-1 receptor ligand;
2) separately measuring the levels of P-glycoprotein expression in the control cell and test cell; and
3) detecting a reduction in P-glycoprotein expression in the test cell by comparing P-glycoprotein expression in the control cell.

18. The method of claim 17, wherein the composition is selected from the group consisting of synthetic combinatorial libraries of small molecule ligands, eukaryotic whole cell lysates or extracts and media conditioned by cultured eukaryotic cells.

19. A method of screening agents for sigma-1 receptor binding activity comprising the steps of:

1) contacting a potential sigma-1 receptor ligand test agent with a test cell that expresses the sigma-1 receptor and high levels of P-glycoprotein;
2) binding the agent to the sigma-1 receptor; and
3) detecting a reduction in P-glycoprotein expression in the test cell.

20. The method of claim 19, wherein the agent is obtained from a composition selected from the group consisting of synthetic combinatorial libraries of small molecule ligands, eukaryotic whole cell lysates or extracts and media conditioned by cultured eukaryotic cells.

21. A method of obtaining and/or generating data related to drug sensitivity using the method of claim 17.

22. A method of obtaining and/or generating data related to drug sensitivity using the method of claim 17 and an automated data acquisition system.

23. A method of screening compositions for chemotherapeutic tolerance-reducing activity comprising the steps of:

1) treating a control chemotherapeutic-sensitive cell and a chemotherapeutic-resistant test cell with said chemotherapeutic agent;

2) contacting the test cell with a composition potentially comprising a sigma-1 receptor ligand;

3) separately measuring the level of chemotherapeutic sensitivity in the control cell and test cell; and

4) detecting an increase in sensitivity in the test cell.

24. The method of claim 23, wherein the chemotherapeutic agent is selected from the group consisting of actinomycin D, doxorubicin, mitoxantrone, paclitaxel and vincristine.

25. The method of claim 23, wherein the chemotherapeutic agent is doxorubicin.

26. The method of claim 23, wherein the chemotherapeutic agent is paclitaxel.